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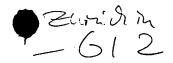
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(54) Title: FORMULATIONS FOR DELIVERY OF OSTEOGENIC PROTEINS

(57) Abstract

A composition is disclosed comprising a pharmaceutically acceptable admixture of an osteogenic protein; a porous particulate polymer matrix; an osteogenic protein-sequestering amount of blood clot; and a calcium sulfate hemihydrate-containing substance. Also disclosed are formulations of bone morphogenetic proteins with improved solubility and/or stability characteristics.

What is claimed is:

1. A composition comprising a pharmaceutically acceptable admixture of

- (i) an osteogenic protein;
- (ii) a porous particulate polymer matrix;
- (iii) an osteogenic protein-sequestering amount of autogenous blood; and
- (iv) a calcium sulfate hemihydrate-containing substance.
- 2. The composition of claim 1 wherein the osteogenic protein is selected from the group consisting of the members of the BMP-family.
- 3. The composition of claim 2 wherein the osteogenic protein is BMP-2.
- 4. The composition of claim 1 wherein the calcium sulfate hemihydrate-containing substance is Plaster of Paris.
- 5. The composition of claim 1 wherein the calcium sulfate hemihydrate-containing substance is a mixture of Plaster of Paris and hydroxyapatite.
- 6. The composition of claim 1 wherein the admixture is free from antifibrinolytic agents.
- 7. The composition of claim 2 wherein the admixture is free from antifibrinolytic agents.
- 8. The composition of claim 3 wherein the admixture is free from antifibrinolytic agents.
- 9. A composition comprising a pharmaceutically acceptable admixture of
 - (i) BMP-2;
 - (ii) a polymeric matrix component comprising porous particles having a diameter of between about 150 and 850 microns and a porosity such that the surface area of the particles is between about 0.01 and 4.0 m²/g;
 - (iii) a protein sequestering amount of autogenous blood;

and

(iv) a calcium sulfate hemihydrate-containing substance.

- 10. The composition of claim 9, wherein the polymer is selected from the group consisting of poly(lactic acid), poly(glycolic acid), and copolymers of lactic acid and glycolic acid.
- 11. The composition of claim 9 wherein the calcium sulfate hemihydrate-containing substance is Plaster of Paris.
- 12. The composition of claim 9 wherein the calcium sulfate hemihydrate-containing substance is a mixture of Plaster of Paris and hydroxyapatite.
- 13. A kit for the repair of cartilage and/or bone injuries which comprises:
 - (i) an osteogenic protein;
 - (ii) a porous particulate polymer matrix; and
 - (iii) a calcium sulfate hemihydrate-containing substance.
- 14. The kit of claim 13 wherein the calcium sulfate hemihydrate-containing substance is Plaster of Paris.
- 15. The composition of claim 13 wherein the calcium sulfate hemihydrate-containing substance is a mixture of Plaster of Paris and hydroxyapatite.
- 16. A composition comprising a pharmaceutically acceptable admixture of
 - (i) an osteogenic protein;
 - (ii) a porous particulate polymer matrix;
 - (iii) a protein-sequestering agent; and
- (iv) an antibiotic substance selected from the group consisting of vancomycin and gentamycin.
- 17. The composition of claim 16, wherein the protein-sequestering agent is selected from the group consisting of cellulosic materials, hyaluronic acid, alginates, autogenous blood, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer, and poly(vinyl alcohol).
- 18. The composition of claim 17, wherein the protein sequestering agent is a cellulosic material selected from the group

consisting of alkylcelluloses (including hydroxy-alkylcelluloses), such as methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose.

- 19. The composition of claim 18, wherein the cellulosic material is diluted with aqueous glycerol.
- 20. A composition comprising a pharmaceutically acceptable admixture of
 - (i) an osteogenic protein;

. . .

; ' '

- (ii) a calcium sulfate hemihydrate-containing substance; wherein said admixture is diluted in aqueous solution, the components of said admixture being present in relative amounts of about 1 gram of osteogenic protein; about 12 grams of calcium sulfate hemihydrate-containing substance; and about 3 ml water.
- 21. A composition comprising an osteogenic protein, about 0.1 to about 5.0% (w/v) of a sugar, about 1.0 to about 10.0% (w/v) glycine, and about 1 to about 20 mM of glutamic acid hydrochloride, wherein such formulation has a pH of about 4.5.
- 22. The formulation of claim 21, further comprising about 0.01 to about 0.1 % (w/v) of a non-ionic surfactant.
- 23. A composition comprising an osteogenic protein, about 1 to about 10% (w/v) glycine, about 0.1 to about 5.0% (w/v) sucrose about 0.01 to about 0.1% (w/v) non-ionic surfactant and about 5 to about 10 mM glutamic acid hydrochloride, wherein such formulation has a pH less than about 6.0.
- 24. A composition comprising an osteogenic protein, about 2.5% (w/v) glycine, about 0.5% (w/v) sucrose, about 5 mM glutamic acid hydrochloride, and about 0.01% (w/v) polysorbate 80, wherein such formulation has a pH of about 4.5.
- 25. A composition comprising a lyophilized formulation of about 3.12% to about 24.38% (w/w) BMP; about 0.52% to about 10.27% (w/w) glutamic acid hydrochloride; about 38.4% to about 75.7% (w/w) glycine; about 14.28% to about 47.15% (w/w) sucrose; and optionally about 0.15% to about 2.94% (w/w) polysorbate 80.
 - 26. A composition according to claim 25 wherein the

formulation comprises relative weight amounts of about 4.0 mg/ml of BMP-2; about 0.918 mg/ml of glutamic acid hydrochloride; about 25 mg/ml of glycine; about 5 mg/ml of sucrose; and optionally about 0.1 mg/ml of polysorbate 80.

27. A composition according to claim 25 wherein the formulation comprises relative weight amounts of about 2.0 mg/ml of BMP-2; about 0.918 mg/ml of glutamic acid hydrochloride; about 25 mg/ml of glycine; about 5 mg/ml of sucrose; and optionally about 0.1 mg/ml of polysorbate 80.